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=> s ((peptide or protein) (3a) immunogenicity) and computer and (automat? or
library or design)
         31215 PEPTIDE
         13791 PEPTIDES
         36405 PEPTIDE
                 (PEPTIDE OR PEPTIDES)
         94542 PROTEIN
         37259 PROTEINS
        107065 PROTEIN
                 (PROTEIN OR PROTEINS)
          1291 IMMUNOGENICITY
             8 IMMUNOGENICITIES
          1297 IMMUNOGENICITY
                 (IMMUNOGENICITY OR IMMUNOGENICITIES)
           118 (PEPTIDE OR PROTEIN) (3A) IMMUNOGENICITY
        320390 COMPUTER
         35916 COMPUTERS
        333603 COMPUTER
                 (COMPUTER OR COMPUTERS)
        570737 AUTOMAT?
         11230 LIBRARY
          3528 LIBRARIES
         13270 LIBRARY
                 (LIBRARY OR LIBRARIES)
        229580 DESIGN
         13511 DESIGNS
        238517 DESIGN
                 (DESIGN OR DESIGNS)
L1           2 ((PEPTIDE OR PROTEIN) (3A) IMMUNOGENICITY) AND COMPUTER AND
               (AUTOMAT? OR LIBRARY OR DESIGN)

=> d bib 1-2
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L1 ANSWER 1 OF 2 WPIDS (C) 2003 THOMSON DERWENT
AN 2002-723395 [78] WPIDS
DNN N2002-570334 DNC C2002-204884
TI Designing a protein pharmaceutical by deriving parametric equations using experimental data and a **library** of ensemble derived properties, and creating a protein pharmaceutical with the structural characteristics.
DC B04 D16 T01
IN FOX, R O; HILSER, V
PA (FOXR-I) FOX R O; (HILS-I) HILSER V; (TEXA) UNIV TEXAS SYSTEM
CYC 100
PI WO 2002073373 A2 20020919 (200278)* EN 87p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
US 2003032065 A1 20030213 (200314)
ADT WO 2002073373 A2 WO 2002-US9017 20020312; US 2003032065 A1 Provisional US 2001-275259P 20010312, US 2002-96177 20020312
PRAI US 2001-275259P 20010312; US 2002-96177 20020312

L1 ANSWER 2 OF 2 WPIDS (C) 2003 THOMSON DERWENT
AN 2002-164709 [21] WPIDS
DNN N2002-125680 DNC C2002-050941
TI Modulating **immunogenicity** of target **protein** involves identifying and then altering potential amino acid sequences that elicit immune response in host organism.
DC B04 T01
IN CHIRINO, A J; DAHIYAT, B I
PA (XENC-N) XENCOR INC; (CHIR-I) CHIRINO A J; (DAHI-I) DAHIYAT B I
CYC 96
PI WO 2002005146 A2 20020117 (200221)* EN 67p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2001078898 A 20020121 (200234)
US 2002119492 A1 20020829 (200259)
ADT WO 2002005146 A2 WO 2001-US21823 20010710; AU 2001078898 A AU 2001-78898 20010710; US 2002119492 A1 Provisional US 2000-217661P 20000710, US 2001-903378 20010710
FDT AU 2001078898 A Based on WO 200205146
PRAI US 2000-217661P 20000710; US 2001-903378 20010710

d bib,abs,kwic 1,4,5,8,10,11,12,13,14

L2 ANSWER 1 OF 34 USPATFULL
AN 2003:51894 USPATFULL
TI Apparatus and method for designing proteins and protein libraries
IN Desjarlais, John R., Pasadena, CA, UNITED STATES
PA The Penn State Research Foundation (U.S. corporation)
PI US 2003036854 A1 20030220
AI US 2002-71859 A1 20020206 (10)
RLI Continuation of Ser. No. US 2001-877695, filed on 8 Jun 2001, PENDING
PRAI US 2001-266711P 20010206 (60)
DT Utility
FS APPLICATION
LREP PAUL D. GREELEY, ESQ., OHLANDT, GREELEY, RUGGIERO & PERLE, L.L.P., 10th FLOOR, ONE LANDMARK SQUARE, STAMFORD, CT, 06901-2682
CLMN Number of Claims: 17
ECL Exemplary Claim: 1
DRWN 6 Drawing Page(s)
LN.CNT 2411
AB Methodology executed by a computer under the control of a program, said computer including a memory for storing said program, said method comprising the steps of inputting an ensemble of protein backbone scaffolds; applying at least one protein design cycle to each of said scaffolds; and generating a probability matrix derived from a plurality of variable sequences.

SUMM . . . & Mayo, 1997a; Dahiyat et al., 1997b), using parameterized force fields and sophisticated optimization methods such as the Dead-End Elimination (**DEE**) theory (Desmet et al., 1992; Goldstein, 1994). These methods were used successfully to design a sequence that adopts the zinc. . .

DETD . . . Also included in the definition of pharmaceutical proteins, are soluble proteins that can serve as vehicles for the delivery of **immunogenic** sequences. Examples of soluble proteins include, but are not limited to, albumins, globulins, other proteins present in the blood and other body fluids, and any other substantially non-**immunogenic** proteins. By "substantially non-**immunogenic** proteins" herein is meant any protein that does not elicit an immune response in a subject. Substantially non-**immunogenic** proteins may be naturally occurring, synthetic, or modified using recombinant techniques known to one of skill in the art. Preferably,. . . (1999) Science, 283:1914-1919; both of which are hereby expressly incorporated by reference), human serum albumin (HSA), IgG, and other substantially non-**immunogenic** proteins.

DETD . . . Lazar et al., 1997) and Monte Carlo searches (Kuhiman & Baker, 2000; Voigt et al., 2000), while deterministic methods include **DEE** (Dahiyat & Mayo, 1996; Desmet et al., 1992) or Self-Consistent Mean Field Theory (Koehl & Delarue, 1996; Lee, 1994; Voigt. . .

DETD . . . antibodies, if the desired epitope is small, the designed protein may be fused to a carrier protein to form an **immunogen**. Alternatively, the designed protein may be made as a fusion protein to increase expression, or for other reasons. For example,. . .

DETD . . . members (for example, its substrates, if it is an enzyme), activity profiles, stability profiles (pH, thermal, buffer conditions), substrate specificity, **immunogenicity**, toxicity, etc.

L2 ANSWER 4 OF 34 USPATFULL
AN 2003:30338 USPATFULL
TI Protein design automation for designing protein libraries with altered **immunogenicity**
IN Chirino, Arthur J., Camarillo, CA, UNITED STATES
Dahiyat, Bassil I., Altadena, CA, UNITED STATES
Desjarlais, John, Pasadena, CA, UNITED STATES

PI US 2003022285 A1 20030130
AI US 2002-39170 A1 20020104 (10)
RLI Continuation-in-part of Ser. No. US 2001-903378, filed on 10 Jul 2001, PENDING
DT Utility
FS APPLICATION
LREP Robin M. Silva, Esq., FLEHR HOHBACH TEST ALBRITTON & HERBERT LLP, Suite 3400, Four Embarcadero Center, San Francisco, CA, 94111-4187
CLMN Number of Claims: 22
ECL Exemplary Claim: 1
DRWN 3 Drawing Page(s)
LN.CNT 3428
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to the use of a variety of computational methods for modulating the **immunogenicity** of proteins by identifying and then altering potential amino acid sequences that elicit an immune response in a host organism. In particular, proteins will be screened for MHC binding sequences, T cell epitopes and B cell epitopes.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Protein design automation for designing protein libraries with altered **immunogenicity**
AB The present invention relates to the use of a variety of computational methods for modulating the **immunogenicity** of proteins by identifying and then altering potential amino acid sequences that elicit an immune response in a host organism.. . .
SUMM [0002] The present invention relates to the use of a variety of computational methods for modulating the **immunogenicity** of proteins by identifying and then altering potential amino acid sequences that elicit an immune response in a host organism.. . .
SUMM . . . Databases consisting of thousands of peptide sequences know to bind MHC molecules have been compiled (Rammensee, H., et al. (1999) **Immunogenetics**, 50:213-219) and several techniques have been developed to analyze the sequences of full length proteins to predict the presence of. . .
SUMM [0012] Reduction of polypeptide **immunogenicity** has been accomplished by using rational site directed mutagenesis (Meyer, et al., (2001) Protein Science 10:491-503), exhaustive site directed mutagenesis. . . be extremely time consuming, especially if considering multiple mutations simultaneously. While rational selection of surface residues can lead to decreased **immunogenicity**, some residue substitutions may be destabilizing and lead to poor folding. In addition, removing solvent exposed charged residues can be. . .
SUMM [0013] One way to overcome these problems is to use computational methods to design sequences that are more or less **immunogenic** relative to a target protein, but retain the structural properties to ensure proper folding and activity.
SUMM . . . methods for screening sequence libraries to select smaller libraries of protein sequences that can be made and evaluated for altered **immunogenicity**.
SUMM [0017] In accordance with the objects outlined above, the present invention provides methods for generating polypeptides exhibiting enhanced **immunogenicity** comprising the steps of inputting a target protein backbone structure with variable residue positions into a computer, computationally generating a. . . least one protein design algorithm, and computationally analyzing said set of primary variant amino acid sequences by applying a computational **immunogenicity** filter. The candidate protein is then made and tested to determine if the **immunogenicity** of the candidate protein is enhanced relative to the target protein. This same method may be used to generate polypeptides exhibiting reduced **immunogenicity**.
SUMM [0018] In an additional aspect, the present invention provides methods for generating polypeptides exhibiting enhanced **immunogenicity** comprising the steps of inputting a target protein backbone structure

with variable residue positions into a computer, applying at least one computational **immunogenicity** filter to generate a set of primary variant amino acid sequences, computationally analyzing said set of primary variant amino acid sequences using at least one protein design algorithm and identifying at least one variant protein with enhanced **immunogenicity**. This same method may be used to generate polypeptides exhibiting reduced **immunogenicity**.

SUMM [0019] In an additional aspect, the present invention provides methods for generating polypeptides exhibiting enhanced **immunogenicity** comprising the steps of inputting a target protein backbone structure with variable residue positions into a computer, computationally generating a. . . sequences by applying at least one protein design algorithm comprising at least one scoring function comprising at least one computational **immunogenicity** filter and identifying at least one variant protein with enhanced **immunogenicity**. This same method may be used to generate polypeptides exhibiting reduced **immunogenicity**.

SUMM [0020] In an additional aspect, the present invention provides methods for generating a polypeptide exhibiting enhanced **immunogenicity** comprising the steps of inputting a target protein backbone structure with variable residue positions into a computer, applying in any order at least one computational protein design algorithm and at least one computational **immunogenicity** filter and identifying at least one variant protein with enhanced **immunogenicity**. This same method may be used to generate polypeptides exhibiting reduced **immunogenicity**.

SUMM . . . positions into a computer, applying in any order at least one computational protein design algorithm and at least one computational **immunogenicity** filter, identifying at least one variant protein with enhanced **immunogenicity**, and administering said variant protein to a patient.

SUMM [0022] The computational design algorithm may be applied prior to or after the application of the computational **immunogenicity** filter. Alternatively, the computational protein design algorithm comprises the computational filter as a scoring function.

SUMM [0023] The computationally generating step, may include applying a computational **immunogenicity** filter comprising a scoring function for MHC class I motifs, MHC class II motifs, B cell epitopes or T cell epitopes. Other computational steps include a Dead-End Elimination (**DEE**) computation, a Monte Carlo search, or use of a genetic algorithm. Additional scoring functions include Van der Waals potential scoring. . .

SUMM [0024] In an additional aspect, the polypeptide may comprise one or more **immunogenic** sequences. The **immunogenic** sequences may be identical or different. The **immunogenic** sequences may be selected from the group consisting of MHC Class I motifs, MHC class II motifs, B cell epitopes. . .

SUMM . . . an additional aspect, the target protein is selected from the group comprising Zn-alpha2-glycoprotein, human serum albumin, immunoglobulin G, and other non-**immunogenic** proteins.

DETD . . . 10.sup.80 or more members) to select smaller libraries of protein sequences (that can comprise up to 10.sup.13 members) with altered **immunogenicity**. For example, if a protein with reduced **immunogenicity** is desired, a computational filter can be use to identify and replace residues known to elicit a immune response with compensatory residues that maintain the native fold and stability of the protein resulting in a protein that is non-**immunogenic** or less **immunogenic** than the starting protein.

DETD [0032] Alternatively, it may be desirable to design proteins with increased **immunogenicity**. In this case, the computational filter can be applied to modify residues to introduce an antigenic motif to ensure proper. . .

DETD . . . property such as stability. Then a computational filter is applied to select those variants with a high propensity for altered

immunogenicity.

DETD [0034] Alternatively, the computational filter is first applied to generate a list of variants with a propensity for altered **immunogenicity**, and then computational processing is done to select those variant that are likely to fold or to be stable.

DETD . . . be searched and used to identify potential MHC class I or class II binding sequences (Rammensee, H., et al. (1999) **Immunogenetics**, 50:213-219). Computational methods are then used to structurally and chemically compensate for amino acid residues involved in binding to MHC molecules. For example, if a variant protein that is less **immunogenic** then the target protein is desired, computational methods can be used identify peptide sequences or amino acid residues predicted to elicit an immune response, replace these residues with residues predicted to be non **immunogenic** and then screen the resulting sequences for sequences that fold properly and are stable.

DETD [0037] There are also situations where it is desirable to increase the **immunogenicity** of a target protein. For example, activating populations of T cells toward a specific epitope has implications for controlling or. . .

DETD [0038] Accordingly, the present invention provides methods for modulating the **immunogenicity** of a target protein. By "modulating" herein is meant that the immune response to a target protein is altered. That. . .

DETD [0039] It should also be noted that altered **immunogenicity** is defined within a particular host organism. That is, in a preferred embodiment, target proteins (as defined below) are altered to exhibit altered **immunogenicity** within a human. Alternate host organisms include, but are not limited to, rodents, (rats, mice, hamster, guinea pigs, etc.), primates,. . .

DETD [0040] By "**immunogenicity**" herein refers to the ability of a protein to elicit an immune response. The ability of a protein to elicit an immune response depends on the amino acid sequence or sequences within the protein. **Immunogenicity** includes both the humoral and the cellular component of the immune response as outlined below. Amino acid sequences capable of eliciting an immune response are referred to herein as "**immunogenic** sequences". Preferably **immunogenic** sequences comprise "MHC binding sites (i.e., MHC binding motifs)", "T cell epitopes" and "B cell epitopes" as outlined below.

DETD [0041] As defined herein, the definition of **immunogenicity** is sufficiently broad to include the term "antigenicity". "Antigenicity" refers to the ability of a protein by itself to elicit. . .

DETD [0042] The response elicited by a protein with an **immunogenic** sequence involves both components of the immune system: the humoral component and the cellular component. Thus, "immune response" in the context of the invention includes any component of the humoral or cellular immune response. Briefly, when a protein with **immunogenic** sequences is administered to a human, that protein is subjected to surveillance by both the humoral and cellular arms of. . . to the protein if it is recognized as foreign and if the immune system is not already tolerant to the **immunogenic** sequence within the protein. For the humoral immune response, immature B cells displaying surface immunoglobulins (Igs) can bind to one. . .

DETD . . . differentiation to antibody producing cells. As can be seen from the above discussion, an effective primary immune response to an **immunogenic** protein generally requires a combination of B and T cell responses to B and T cell specific sequences or epitopes.

DETD [0044] Alternatively, if the **immunogenic** sequences are specific for MHC class I molecules, the MHC I antigen processing/presentation pathways are involved. MHC class I molecules. . . the TCRs of cytotoxic T lymphocytes and are the primary antigenic determinants of the cellular immune response. Thus, modulation of **immunogenicity** includes identifying peptides that stimulate T

cell responses, termed T cell epitopes, changing the sequence of these peptides such that the cellular response to the protein is either reduced or enhanced. Additionally, modulation of **immunogenicity** also includes identifying peptides that stimulate B cell responses, termed "B cell epitopes" or "BCRs", changing the sequence of these. . .

DETD [0049] Accordingly, the present invention is directed to methods for modulating the **immunogenicity** of a target protein. By "target protein" herein is meant at least two covalently attached amino acids, which includes proteins,. . .

DETD [0063] Thus, by "target protein" herein is meant a protein for which a library of variants, preferably with altered **immunogenicity** is desired. As will be appreciated by those in the art, any number of target proteins will find use in. . .

DETD . . . Also included in the definition of pharmaceutical proteins, are soluble proteins that can serve as vehicles for the delivery of **immunogenic** sequences. Examples of soluble proteins include, but are not limited to, albumins, globulins, other proteins present in the blood and other body fluids, and any other substantially non-**immunogenic** proteins. By "substantially non-**immunogenic** proteins" herein is meant any protein that does not elicit an immune response in a subject. Substantially non-**immunogenic** proteins may be naturally occurring, synthetic, or modified using recombinant techniques known to one of skill in the art. Preferably,. . . (1999) Science, 283:1914-1919; both of which are hereby expressly incorporated by reference), human serum albumin (HSA), IgG, and other substantially non-**immunogenic** proteins.

DETD . . . the calculations either unwieldy or impossible in real time. Accordingly, to solve this combinatorial search problem, a "Dead End Elimination" (**DEE**) calculation is performed. The **DEE** calculation is based on the fact that if the worst total interaction of a first rotamer is still better than. . . rotamer cannot be part of the global optimum solution. Since the energies of all rotamers have already been calculated, the **DEE** approach only requires sums over the sequence length to test and eliminate rotamers, which speeds up the calculations considerably. **DEE** can be rerun comparing pairs of rotamers, or combinations of rotamers, which will eventually result in the determination of a. . .

DETD . . . found, a Monte Carlo search may be done to generate a rank-ordered list of sequences in the neighborhood of the **DEE** solution. Starting at the **DEE** solution, random positions are changed to other rotamers, and the new sequence energy is calculated. If the new sequence meets. . .

DETD . . . processing may occur. As outlined in U.S. Ser. No. 09/127,926 and PCT US98/07254, preferred embodiments utilize a Dead End Elimination (**DEE**) step, and preferably a Monte Carlo step.

DETD [0115] In a preferred embodiment, a variety of process filtering techniques can be done, including, but not limited to, **DEE** and its related counterparts. Additional filtering techniques include, but are not limited to branch-and-bound techniques for finding optimal sequences (Gordon. . .

DETD . . . that differs from the target protein in at least one MHC, TCR, or BCR binding site. Preferably, if a less **immunogenic** protein is desired, the candidate variant protein differs from the target protein by the elimination of at least one MHC, TCR, or BCR binding site. Alternatively, if a more **immunogenic** protein is desired, the candidate variant protein differs from the target protein via the addition of at least one MHC,. . .

DETD [0128] In a preferred embodiment, a computational **immunogenicity** filter is applied to the set of primary library sequences. By "computational **immunogenicity** filter" herein is meant any one of a number of scoring functions derived from data on binding of peptides to MHC molecules, or T cell epitopes or B cell epitopes. The computational **immunogenecity** filter can be applied as part of

the original computation (e. g., substantially simultaneously; for example as one of the. . . as a pre-filter), or after the original computation (e.g., as a post-filter). For example, in a preferred embodiment, the computational **immunogenicity** filter is used as a post-filter: that is, the scoring functions are used to rescore the set of primary library sequences to eliminate potentially **immunogenic** sequences, or to introduce non-**immunogenic** sequences.

DETD [0129] In a preferred embodiment, the computational **immunogenicity** filter is applied during the same time, i.e., substantially simultaneously, when the primary library sequences are generated.

DETD [0130] In other preferred embodiments, the computational **immunogenicity** filter is applied before the computational generation of a set of primary sequences. Using this approach, a set of primary sequences is generated that potentially either lack or include **immunogenic** sequences depending on the desired result. The PDA.TM. technology is then run on these sequences to identify those sequences that. . .

DETD . . . molecules have been compiled (Buus, supra; Brusic, V., et al., (1998) Nucleic Acids Res., 26:368-371; Rammensee, H-G., et al., (1999) **Immunogenetics**, 50:213-219) and several techniques have been developed to analyze sequences of full length proteins to predict the presence of potentially **immunogenic** sequences (Hiemstra, H. S. et al. (2000) Curr. Op. Immunol., 12:80-84; Malios, R. R., (1999) Bioinformatics, 15:432-439; Sturniolo, T., et. . .

DETD . . . MHCPEP, are also available and may be used to identify potential MHC I binding sites (Rammensee, H-G., et al., (1999) **Immunogenetics**, 50:213-219; Brusic, V., et al., (1998) Nucleic Acids Research, 26:368-371; hereby incorporated by reference in their entirety). Other methods for. . .

DETD . . . motifs will be identified either by matching a database of published motifs, such as SYFPEITHI (Rammensee, H., et al., (1999) **Immunogenetics**, 50:213-219; http://134.2.96.221/scripts/MHCServe r.dll/home.html)); http://wehih.wehi.edu.au/mhcpep/, MHCEP (Brusic, B., et al., supra) or by either established methods such as neural net (Gulukota, K,. . .

DETD . . . the one described by Kutter, C., et al., (2000) J. Mol. Biol., 298:417-429 and Nussbaum, A. K., et al., (2001) **Immunogenetics**, 53:87-94; both of which are incorporated by reference in their entirety.

DETD . . . motifs will be identified either by matching a database of published motifs, such as SYFPEITHI (Rammensee, H., et al., (1999) **Immunogenetics**, 50:213-219; http://134.2.96.221/scripts/MHCServe r.dll/home.html)); http://wehih.wehi.edu.au/mhcpep/, MHCEP (Brusic, B., et al., supra) or by established methods such as neural net (Gulukota, K, supra),. . .

DETD . . . the one described by Kutter, C., et al., (2000) J. Mol. Biol., 298:417429 and Nussbaum, A. K., et al., (2001) **Immunogenetics**, 53:87-94; both of which are incorporated by reference in their entirety.

DETD . . . the class I ligands, the nonanchoring amino acids play a secondary, but still significant role (Rammensee, H., et al., (1999) **Immunogenetics**, 50:213-219). Rules for identifying MHC II binding sites have been described in Hammer, J. et al., (1994) Behring. Inst. Mitt.,. . .

DETD . . . binding sites will be identified by matching a database of published motifs, such as SYFPEITHI (Rammensee, H., et al., (1999) **Immunogenetics**, 50:213-219;

DETD . . . motifs will be identified either by matching a database of published motifs, such as SYFPEITHI (Rammensee, H., et al., (1999) **Immunogenetics**, 50:213-219; http://134.2.96.221/scripts/MHCServe r.dll/home.html)); http://wehih.wehi.edu.au/mhcpep/, MHCEP (Brusic, B., et al., supra) or by established methods such as virtual matrices (Sturniolo, T, et. . .

DETD . . . to antibodies. In a preferred embodiment, potential B cell epitopes will be replaced with smaller neutral residues to reduce the **immunogenicity** of the sequence as described by Meyer et al. (Meyer, D. L., et al. (2001), Protein Sci., 10:491-503; see also. . .

DETD [0192] In addition, in some embodiments, it is desirable to have candidate variant proteins with altered **immunogenicity** that are more stable than the target protein. Preferably, it would be desirable have proteins that exhibit oxidative stability, alkaline. . .

DETD . . . antibodies, if the desired epitope is small, the library protein may be fused to a carrier protein to form an **immunogen** . Alternatively, the library protein may be made as a fusion protein to increase expression, or for other reasons. For example,. . .

DETD [0253] Once expressed and purified if necessary, the candidate variant library proteins and nucleic acids can be tested for altered **immunogenicity**. Suitable methods include measuring of the binding of MHC peptide complexes to TCRs, measurement of MHC/peptide interactions(Sidney, J., et al.,. . .

DETD . . . of the invention find use in a number of applications. In a preferred embodiment, candidate variant proteins that are less **immunogenic** than the target protein are used as therapeutic proteins. For example, clinical and preclinical therapy studies have shown that exogenous. . . the activation of pro-drugs (Meyer, D L., et al. (2001) Protein Science, 10:491-503). Other uses for therapeutic proteins with reduced **immunogenicity** includes thrombolytic therapy of acute myocardial infarction (Laroche, Y., et al., (2000) Blood, 96:1425-1432).

DETD [0255] In a preferred embodiment, candidate variant proteins that are more **immunogenetic** than the target protein are used in the development of vaccines and immunotherapeutics for autoimmune disease and cancer. For example,. . .

DETD [0264] In other embodiments, the candidate variant proteins are more **immunogenic** toward different cancers including solid tumors such as skin, breast, brain, cervical carcinomas, testicular carcinomas, etc. More particularly, cancers that. . .

DETD [0274] Combinations of pharmaceutical compositions may be administered. For example, pharmaceutical compositions comprising mixtures of variant proteins exhibiting enhanced **immunogenicity** selected from the group consisting of variants of soluble proteins such as, zinc-alpha2-glycoprotein, human serum albumin, immunoglobulin G (IgG) and other modified non-**immunogenic** proteins may be administered to a patient. Moreover, the compositions may be administered in combination with other therapeutics.

DETD . . . vaccines include a gene encoding an adjuvant molecule with the DNA vaccine. Such adjuvant molecules include cytokines that increase the **immunogenic** response to the variant polypeptide encoded by the DNA vaccine. Additional or alternative adjuvants are known to those of ordinary. . .

CLM What is claimed is:

1. A method for generating a polypeptide exhibiting enhanced **immunogenicity**, said method comprising: a) inputting a target backbone structure with variable residue positions into a computer; b) applying, in any order: i) at least one computational protein design algorithm; and ii) at least one computational **immunogenicity** filter; and c) identifying at least one variant protein with enhanced **immunogenicity**.

2. A method for generating a polypeptide exhibiting reduced **immunogenicity**, said method comprising: a) inputting a target backbone structure with variable residue positions into a computer; b) applying, in any order: i) at least one computational protein design algorithm; and ii) at least one computational **immunogenicity** filter; and c) identifying at least one variant protein with reduced **immunogenicity**.

. . . computer; b) applying, in any order: i) at least one computational protein design algorithm; and ii) at least one computational **immunogenicity** filter; c) identifying at least one variant protein with enhanced **immunogenicity**; and d) administering said variant protein to a patient.

. . . or 3 wherein said target protein is selected from the group consisting of Zn-alpha2-glycoprotein, human serum albumin, immunoglobulin G and non-**immunogenic** proteins.

8. A method according to claim 1, 2, or 3 wherein said computational **immunogenicity** filter comprises a scoring function for MHC class I motifs.

9. A method according to claim 1, 2, or 3 wherein said computational **immunogenicity** filter comprises a scoring function for MHC class II motifs.

10. A method according to claim 1, 2, or 3 wherein said enhanced **immunogenicity** is due to the presence of at least one **immunogenic** sequence.

11. A method according to claim 10 wherein said **immunogenic** sequences are the same.

12. A method according to claim 10 wherein said **immunogenic** sequences are different.

13. A method according to claim 10, 11, or 12 wherein said **immunogenic** sequence is selected from the group consisting of B cell epitopes, T cell epitopes, MHC class I motifs and MHC. . .

14. A method according to claim 10 wherein said **immunogenic** sequence further comprises a specific cleavage motif.

15. A method according to claim 1, 2 or 3 wherein said computationally generating step comprises a **DEE** computation.

16. A method according to claim 15 wherein said **DEE** computation is selected from the group consisting of original **DEE** and Goldstein **DEE**.

21. A modified polypeptide exhibiting enhanced **immunogenicity** made by the method according to claim 1, 2 or 3.

. . . 3 wherein said variant protein is selected from the group consisting of variants of Zn-alpha2-glycoprotein, human serum albumin, immunoglobulin G, non-**immunogenic** proteins, and mixtures thereof.

L2 ANSWER 5 OF 34 USPATFULL
AN 2002:323761 USPATFULL
TI Method for the generation of proteins with new enzymatic function
IN Mayo, Stephen, Pasadena, CA, UNITED STATES
Bolon, Daniel N., Pasadena, CA, UNITED STATES
PI US 2002183937 A1 20021205
AI US 2002-74679 A1 20020211 (10)
PRAI US 2001-267602P 20010209 (60)
DT Utility
FS APPLICATION
LREP ROBIN M. SILVA, ESQ., FLEHR HOHBACH TEST ALBRITTON & HERBERT LLP, Four Embarcadero Center - Suite 3400, San Francisco, CA, 94111-4187
CLMN Number of Claims: 17
ECL Exemplary Claim: 1

DRWN 9 Drawing Page(s)
LN.CNT 2633
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to the use of a variety of computational methods for generating enzyme-like protein catalysts. Specifically, computational methods are used to insert active site domains, including catalytic domains and binding domains, into a protein scaffold and optimize surrounding amino acids for interaction with the active site domain.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . protein sequences include PDA.TM., sequence prediction algorithm, and force field calculations. The protein design cycle may include a Dead-End Elimination (**DEE**) computation. Generally, the analyzing step includes the use of at least one scoring function selected from the group consisting of. . .

DETD [0046] Suitable scaffolds include thioredoxin (Holmgren, A., (1985) Annu Rev Biochem, 237-271), human serum albumin, non **immunogenic** soluble proteins, such as Zn-alpha2-glycoprotein (Sanchez, L. M., (1997) Proc. Natl. Acad. Sci., 94:4626-4630; Sanchez, L. M., et al., (1999). . .

DETD . . . the calculations either unwieldy or impossible in real time. Accordingly, to solve this combinatorial search problem, a "Dead End Elimination" (**DEE**) calculation is performed. The **DEE** calculation is based on the fact that if the worst total interaction of a first rotamer is still better than. . . rotamer cannot be part of the global optimum solution. Since the energies of all rotamers have already been calculated, the **DEE** approach only requires sums over the sequence length to test and eliminate rotamers, which speeds up the calculations considerably. **DEE** can be rerun comparing pairs of rotamers, or combinations of rotamers, which will eventually result in the determination of a. . .

DETD . . . found, a Monte Carlo search may be done to generate a rank-ordered list of sequences in the neighborhood of the **DEE** solution. Starting at the **DEE** solution, random positions are changed to other rotamers, and the new sequence energy is calculated. If the new sequence meets. . .

DETD . . . processing may occur. As outlined in U.S. Ser. No. 09/127,926 and PCT US98/07254, preferred embodiments utilize a Dead End Elimination (**DEE**) step, and preferably a Monte Carlo step. PDA.TM. technology, viewed broadly, has three components that may be varied to alter. . .

DETD [0100] In a preferred embodiment, a variety of process filtering techniques can be done, including, but not limited to, **DEE** and its related counterparts. Additional filtering techniques include, but are not limited to branch-and-bound techniques for finding optimal sequences (Gordon. . .

DETD . . . antibodies, if the desired epitope is small, the library protein may be fused to a carrier protein to form an **immunogen** . Alternatively, the library protein may be made as a fusion protein to increase expression, or for other reasons. For example,. . .

DETD . . . order to accommodate the substrate and to build the active site. After computing the optimal solution using algorithms based on **DEE**, positions that changed to alanine can be subsequently allowed to change identity to other amino acids in order to form. . .

CLM What is claimed is:
10. A method according to claim 1 wherein said protein design cycle comprises a **DEE** computation

L2 ANSWER 8 OF 34 USPATFULL
AN 2002:221352 USPATFULL
TI Protein design automation for designing protein libraries with altered **immunogenicity**

IN Chirino, Arthur J., Camarillo, CA, UNITED STATES
Dahiyat, Bassil I., Altadena, CA, UNITED STATES
PI US 2002119492 A1 20020829
AI US 2001-903378 A1 20010710 (9)
PRAI US 2000-217661P 20000710 (60)
DT Utility
FS APPLICATION
LREP FLEHR HOHBACH TEST ALBRITTON & HERBERT LLP, Suite 3400, Four Embarcadero Center, San Francisco, CA, 94111-4187
CLMN Number of Claims: 18
ECL Exemplary Claim: 1
DRWN 3 Drawing Page(s)
LN.CNT 3014
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to the use of a variety of computational methods for modulating the **immunogenicity** of proteins by identifying and then altering potential amino acid sequences that elicit an immune response in a host organism. In particular, proteins will be screened for MHC binding sequences, T cell epitopes and B cell epitopes.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Protein design automation for designing protein libraries with altered **immunogenicity**
AB The present invention relates to the use of a variety of computational methods for modulating the **immunogenicity** of proteins by identifying and then altering potential amino acid sequences that elicit an immune response in a host organism.. . .
SUMM [0002] The present invention relates to the use of a variety of computational methods for modulating the **immunogenicity** of proteins by identifying and then altering potential amino acid sequences that elicit an immune response in a host organism.. . .
SUMM . . . Databases consisting of thousands of peptide sequences know to bind MHC molecules have been compiled (Rammensee, H., et a. (1999) **Immunogenetics**, 50:213-219) and several techniques have been developed to analyze the sequences of full length proteins to predict the presence of. . .
SUMM [0011] Reduction of polypeptide **immunogenicity** has been accomplished by using rational site directed mutagenesis (Meyer, et al., (2001) Protein Science 10:491-503), exhaustive site directed mutagenesis. . . be extremely time consuming, especially if considering multiple mutations simultaneously. While rational selection of surface residues can lead to decreased **immunogenicity**, some residue substitutions may be destablilizing and lead to poor folding. In addition, removing solvent exposed charged residues can be. . .
SUMM [0012] One way to overcome these problems is to use computational methods to design sequences that are more or less **immunogenic** relative to a target protein, but retain the structural properties to ensure proper folding and activity.
SUMM . . . methods for screening sequence libraries to select smaller libraries of protein sequences which can be made and evaluated for altered **immunogenicity**.
SUMM [0016] In accordance with the objects outlined above, the present invention provides methods for modulating the **immunogenicity** of a target protein comprising the steps of inputting a protein backbone structure with variable residue positions into a computer, computationally generating a set of primary variant sequences, and applying a computational **immunogenicity** filter against the set of primary variant sequences to identify at least one candidate variant protein. The candidate protein is then made and tested to determine if the **immunogenicity** of the candidate protein is altered relative to the target protein.
SUMM . . . variable residue position as either a core, surface or boundary residue. The computationally generating step may include a Dead-End Elimination (**DEE**) computation or a Monte Carlo search.

Generally, the primary variant sequences are optimized for at least one scoring function selected. . .

SUMM . . . an additional aspect, the target protein is from a non human species and the candidate variant protein is rendered less **immunogenic** or non **immunogenic** in humans.

SUMM [0019] In an additional aspect, the present invention provides methods for modulating the **immunogenicity** of a target protein comprising the steps of inputting a protein backbone with variable residue positions into a computer, applying a computational **immunogenicity** filter to identify at least one candidate variant protein, computationally analyzing said variant protein for proper folding and stability, and. . .

DETD . . . 10.sup.80 or more members) to select smaller libraries of protein sequences (that can comprise up to 10.sup.13 members) with altered **immunogenicity**. For example, if a protein with reduced **immunogenicity** is desired, a computational filter can be use to identify and replace residues known to elicit a immune response with compensatory residues that maintain the native fold and stability of the protein resulting in a protein that is non-**immunogenic** or less **immunogenic** than the starting protein.

DETD [0026] Alternatively, it may be desirable to design proteins with increased **immunogenicity**. In this case, the computational filter can be applied to modify residues to introduce an antigenic motif to ensure proper. . .

DETD . . . property such as stability. Then a computational filter is applied to select those variants with a high propensity for altered **immunogenicity**.

DETD [0028] Alternatively, the computational filter is first applied to generate a list of variants with a propensity for altered **immunogenicity**, and then computational processing is done to select those variant that are likely to fold or to be stable.

DETD . . . be searched and used to identify potential MHC class I or class II binding sequences (Rammensee, H., et al. (1999) **Immunogenetics**, 50:213-219). Computational methods are then used to structurally and chemically compensate for amino acid residues involved in binding to MHC molecules. For example, if a variant protein that is less **immunogenic** then the target protein is desired, computational methods can be used identify peptide sequences or amino acid residues predicted to elicit an immune response, replace these residues with residues predicted to be non **immunogenic** and then screen the resulting sequences for sequences that fold properly and are stable.

DETD [0031] There are also some situations where it is desirable to increase the **immunogenicity** of a target protein. For example, activating populations of T cells toward a specific epitope has implications for controlling or. . .

DETD [0032] Accordingly, the present invention provides methods for modulating the **immunogenicity** of a target protein. By "modulating" herein is meant that the immune response to a target protein is altered. That. . .

DETD [0033] It should also be noted that altered **immunogenicity** is defined within a particular host organism. That is, in a preferred embodiment, target proteins (as defined below) are altered to exhibit altered **immunogenicity** within a human. Alternate host organisms include, bur are not limited to, rodents, (rats, mice, hamster, guinea pigs, etc.), primates,. . .

DETD [0034] By "**immunogenicity**" herein refers to the ability of a protein to elicit an immune response. The ability of a protein to elicit. . . sequence or sequences within the protein. Amino acid sequences capable of eliciting an immune response are referred to herein as "**immunogenic** sequences". Preferably **immunogenic** sequences comprise "MHC binding sites", "T cell epitopes" and "B cell epitopes" as outlined below.

DETD [0035] As defined herein, the definition of **immunogenicity** is

sufficiently broad to include the term "antigenicity". "Antigenicity" refers to a the ability of a protein by itself to. . .

DETD [0036] The response elicited by a protein with an **immunogenic** sequence involves both components of the immune system: the humoral component and the cellular component. Thus, "immune response" in the. . .

DETD [0037] Briefly, when a protein with **immunogenic** sequences is administered to a human, that protein is subjected to surveillance by both the humoral and cellular arms of. . . to the protein if it is recognized as foreign and if the immune system is not already tolerant to the **immunogenic** sequence within the protein. For the humoral immune response, immature B cells displaying surface immunoglobulins (Igs) can bind to one. . .

DETD . . . differentiation to antibody producing cells. As can be seen from the above discussion, an effective primary immune response to an **immunogenic** protein generally requires a combination of B and T cell responses to B and T cell specific sequences or epitopes.

DETD [0039] Alternatively, if the **immunogenic** sequences are specific for MHC class I molecules, the MHC I antigen processing/presentation pathways are involved. MHC class I molecules. . . the TCRs of cytotoxic T lymphocytes and are the primary antigenic determinants of the cellular immune response. Thus, modulation of **immunogenicity** includes identifying peptides that stimulate T cell responses, termed T cell epitopes, changing the sequence of these peptides such that the cellular response to the protein is either reduced or enhanced. Additionally, modulation of **immunogenicity** also includes identifying peptides that stimulate B cell responses, termed "B cell epitopes" or "BCRs", changing the sequence of these. . .

DETD [0045] Accordingly, the present invention is directed to methods for modulating the **immunogenicity** of a target protein. By "target protein" herein is meant at least two covalently attached amino acids, which includes proteins,. . .

DETD [0060] Thus, by "target protein" herein is meant a protein for which a library of variants, preferably with altered **immunogenicity** is desired. As will be appreciated by those in the art, any number of target proteins find use in the. . .

DETD . . . the calculations either unwieldy or impossible in real time. Accordingly, to solve this combinatorial search problem, a "Dead End Elimination" (**DEE**) calculation is performed. The **DEE** calculation is based on the fact that if the worst total interaction of a first rotamer is still better than. . . rotamer cannot be part of the global optimum solution. Since the energies of all rotamers have already been calculated, the **DEE** approach only requires sums over the sequence length to test and eliminate rotamers, which speeds up the calculations considerably.

DETD [0087] **DEE** can be rerun comparing pairs of rotamers, or combinations of rotamers, which will eventually result in the determination of a. . .

DETD . . . found, a Monte Carlo search may be done to generate a rank-ordered list of sequences in the neighborhood of the **DEE** solution. Starting at the **DEE** solution, random positions are changed to other rotamers, and the new sequence energy is calculated. If the new sequence meets. . .

DETD . . . processing may occur. As outlined in U.S. Ser. No. 09/127,926 and PCT US98/07254, preferred embodiments utilize a Dead End Elimination (**DEE**) step, and preferably a Monte Carlo step.

DETD [0114] In a preferred embodiment, a variety of process filtering techniques can be done, including, but not limited to, **DEE** and its related counterparts. Additional filtering techniques include, but are not limited to branch-and-bound techniques for finding optimal sequences (Gordon. . .

DETD . . . that differs from the target protein in at least one MHC, TCR, or BCR binding site. Preferably, if a less **immunogenic** protein

is desired, the candidate variant protein differs from the target protein by the elimination of at least one MHC, TCR, or BCR binding site. Alternatively, if a more **immunogenic** protein is desired, the candidate variant protein differs from the target protein via the addition of at least one MHC,. . .

DETD [0127] In a preferred embodiment, a computational **immunogenicity** filter is applied to the set of primary library sequences. By "computational **immunogenicity** filter" herein is meant a any one of a number of scoring functions derived from data on binding of peptides. . . or B cell epitopes. These scoring functions are used to rescore the set of primary library sequences to eliminate potentially **immunogenic** sequences, or eliminate non-**immunogenic** sequences. PDA will then be used to structurally and chemically compensate for any residues, including surface residues, removed or added to modulate **immunogenicity**.

DETD [0130] In other embodiments, the computational **immunogenicity** filter is applied before ir during the computational generation of a set of primary sequences. Using this approach, a set of primary sequences is generated that potentially either lack or include **immunogenic** sequences. PDA.TM. technology is then run on these sequences to identify those sequences that retain the native fold and are. . .

DETD . . . supra) and several techniques have been developed to analyze sequences of full length proteins to predict the presence of potentially **immunogenic** sequences (Hiemstra, H. S. et al. (2000) Curr. Op. Immunol., 12:80-84; Malios, R. R., (1999) Bioinformatics, 15:432-439; Sturniolo, T., et. . .

DETD . . . binding motifs will be identified by matching a database of published motifs, such as SYFPEITHI (Rammensee, H., et al., (1999) **Immunogenetics**, 50:213-219; http://134.2.96.221/scripts/MHCServe r.dll/home.html)); http://wehih.wehi.edu.au/mhcpep/.

DETD . . . the class I ligands, the nonanchoring amino acids play a secondary, but still significant role (Rammensee, H., et al., (1999) **Immunogenetics**, 50:213-219). Rules for identifying MHC II binding sites have been described in Hammer, J. et al., (1994) Behring. Inst. Mitt.,. . .

DETD . . . binding sites will be identified by matching a database of published motifs, such as SYFPEITHI (Rammensee, H., et al., (1999) **Immunogenetics**, 50:213-219; http://134.2.96.221/scripts/MHCServe r.dll/home.html) or http://wehih.wehi.edu.au/mhcpep/). Alternatively, the prediction of binding to class II molecules will use the method of virtual matrices. . .

DETD . . . to antibodies. In a preferred embodiment, potential B cell epitopes will be replaced with smaller neutral residues to reduce the **immunogenicity** of the sequence as described by Meyer et al. (Meyer, D. L., et al. (2001), Protein Sci., 10:491-503; see also. . .

DETD [0178] In addition, in some embodiments, it is desirable to have candidate variant proteins with altered **immunogenicity** that are more stable than the target protein. Preferably, it would be desirable have proteins that exhibit oxidative stability, alkaline. . .

DETD . . . antibodies, if the desired epitope is small, the library protein may be fused to a carrier protein to form an **immunogen** . Alternatively, the library protein may be made as a fusion protein to increase expression, or for other reasons. For example,. . .

DETD [0242] Once expressed and purified if necessary, the candidate variant library proteins and nucleic acids can be tested for altered **immunogenicty**. Suitable methods include measuring of the binding of MHC peptide complexes to TCRs, measurement of MHC/peptide interactions(Sidney, J., et al.,. . .

DETD . . . of the invention find use in a number of applications. In a preferred embodiment, candidate variant proteins that are less **immunogenic** than the target protein are used as therapeutic proteins. For example, clinical and preclinical therapy studies have shown that exogenous. . . for the activation of pro-drugs (Meyer,

DL., et al. (2001) Protein Science, 10:491-503). Other uses for therapeutic proteins with reduced **immunogenicity** includes thrombolytic therapy of acute myocardial infarction (Laroche, Y., et al., (2000) Blood, 96:1425-1432).

DETD [0244] In a preferred embodiment, candidate variant proteins that are more **immunogenetic** than the target protein are used in the development of vaccines and immunotherapeutics for autoimmune disease and cancer. For example,. . .

DETD [0246] In other embodiments, the candidate variant proteins are more **immunogenic** toward tumor cells.

DETD . . . vaccines include a gene encoding an adjuvant molecule with the DNA vaccine. Such adjuvant molecules include cytokines that increase the **immunogenic** response to the variant polypeptide encoded by the DNA vaccine. Additional or alternative adjuvants are known to those of ordinary. . .

CLM What is claimed is:

1. A method for modulating the **immunogenicity** of a target protein, said method comprising: a) inputting a protein backbone structure with variable residue positions of a target. . . protein into a computer; b) computationally generating a set of primary variant amino acid sequences; and, c) applying a computational **immunogenicity** filter against said set to identify at least one candidate variant protein.

2. A method according to claim 1 further comprising testing said candidate variant protein to determine if said **immunogenicity** is altered relative to said target protein.

4. A method according to claim 1 wherein said computationally generating step comprises a **DEE** computation.

5. A method according to claim 4 wherein said **DEE** computation is selected from the group consisting of original **DEE** and Goldstein **DEE**.

10. A method according to claim 1 wherein said target protein is from a non human species and said candidate variant protein exhibits reduced **immunogenicity** in humans.

11. A method according to claim 1 wherein the **immunogenicity** of said candidate variant protein is reduced relative to said target protein.

12. A method according to claim 1 wherein said candidate variant protein is non-**immunogenic**.

14. A method according to claim 1 wherein said modulating the **immunogenicity** of said target protein comprises modifying the amino acid sequence that binds to an MHC molecule.

17. A method according to claim 1 wherein said modulating the **immunogenicity** of said target protein comprises modifying an amino acid sequence encoding a T cell epitope.

18. A method for modulating the **immunogenicity** of a target protein, said method comprising: a) inputting a protein backbone structure with variable residue positions of a target protein into a computer; b) applying a computational **immunogenicity** filter to identify at least one candidate variant protein; d) computationally analyzing said variant protein for maintenance of native fold. . .

L2 ANSWER 10 OF 34 USPATFULL

AN 2002:171899 USPATFULL

TI Protein design automation for protein libraries

IN Dahiyat, Bassil I, Los Angeles, CA, UNITED STATES
Bentzien, Joerg, Pasadena, CA, UNITED STATES
Fiebig, Klaus, Frankfurt, GERMANY, FEDERAL REPUBLIC OF
Hayes, Robert, Pasadena, CA, UNITED STATES

PI US 2002090648 A1 20020711
AI US 2001-927790 A1 20010810 (9)
RLI Continuation-in-part of Ser. No. US 2001-782004, filed on 12 Feb 2001, PENDING Continuation-in-part of Ser. No. US 1999-419351, filed on 15 Oct 1999, PENDING
PRAI US 2000-181630P 20000210 (60)
US 2000-186904P 20000303 (60)
US 2000-197851P 20000414 (60)
US 1999-158700P 19991008 (60)
US 1998-104612P 19981016 (60)
DT Utility
FS APPLICATION
LREP Robin M. Silva, FLEHR HOHBACH TEST ALBRITTON & HERBERT LLP, Suite 3400, Four Embarcadero Center, San Francisco, CA, 94111-4187
CLMN Number of Claims: 9
ECL Exemplary Claim: 1
DRWN 7 Drawing Page(s)
LN.CNT 3366

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention relates to the use of protein design automation (P DA) to generate computationally prescreened secondary libraries of proteins, and to methods and compositions utilizing the libraries.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . the calculations either unwieldy or impossible in real time. Accordingly, to solve this combinatorial search problem, a "Dead End Elimination" (**DEE**) calculation is performed. The **DEE** calculation is based on the fact that if the worst total interaction of a first rotamer is still better than. . . rotamer cannot be part of the global optimum solution. Since the energies of all rotamers have already been calculated, the **DEE** approach only requires sums over the sequence length to test and eliminate rotamers, which speeds up the calculations considerably. **DEE** can be rerun comparing pairs of rotamers, or combinations of rotamers, which will eventually result in the determination of a. . .

DETD . . . found, a Monte Carlo search may be done to generate a rank-ordered list of sequences in the neighborhood of the **DEE** solution. Starting at the **DEE** solution, random positions are changed to other rotamers, and the new sequence energy is calculated. If the new sequence meets. . .

DETD . . . processing may occur. As outlined in U.S. Ser. No. 09/127,926 and PCT US98/07254, preferred embodiments utilize a Dead End Elimination (**DEE**) step, and preferably a Monte Carlo step.

DETD . . . used to rescore a library in order to eliminate proteins containing sequences which can potentially bind to MHC, i.e. potentially **immunogenic** sequences.

DETD [0092] In a preferred embodiment, a variety of filtering techniques can be done, including, but not limited to, **DEE** and its related counterparts. Additional filtering techniques include, but are not limited to branch-and-bound techniques for finding optimal sequences (Gordon. . .

DETD . . . these methods, including, but not limited to, enzyme activity, stability, solubility, aggregation, binding affinity, binding specificity, substrate specificity, structural integrity, **immunogenicity**, toxicity, generate peptide and peptidomimmetic libraries, create new antibody CDR's, generate new DNA, RNA bindings, etc.

DETD . . . have residues in the hydrophobic cores screened, to prevent changes in the molecular surface of the protein that might induce **immunogenic** responses. Therapeutic proteins can also be designed

in the region surrounding their binding sites to their receptors. Such a region. . .

DETD . . . antibodies, if the desired epitope is small, the library protein may be fused to a carrier protein to form an **immunogen**. Alternatively, the library protein may be made as a fusion protein to increase expression, or for other reasons. For example,. . .

DETD . . . members (for example, its substrates, if it is an enzyme), activity profiles, stability profiles (pH, thermal, buffer conditions), substrate specificity, **immunogenicity**, toxicity, etc.

DETD [0263] The Dead End Elimination (**DEE**) optimization method (see reference) was used to find the lowest energy, ground state sequence. **DEE** cutoffs of 50 and 100 kcal/mol were used for singles and doubles energy calculations, respectively.

DETD [0264] Starting from the **DEE** ground state sequence, a Monte Carlo (MC) calculation was performed that generated a list of the 1000 lowest energy sequences.. . .

L2 ANSWER 11 OF 34 USPATFULL
AN 2002:136760 USPATFULL
TI Protein design automatic for protein libraries
IN Dahiyat, Bassil I., Los Angeles, CA, United States
Hayes, Robert J., Altadena, CA, United States
Bentzien, Jorg, Pasadena, CA, United States
Fiebig, Klaus M., Frankfurt, GERMANY, FEDERAL REPUBLIC OF
PA Xencor, Monrovia, CA, United States (U.S. corporation)
PI US 6403312 B1 20020611
AI US 1999-419351 19991015 (9)
RLI Continuation-in-part of Ser. No. US 2000-564961, filed on 4 May 2000
PRAI US 1998-104612P 19981016 (60)
US 1999-132475P 19990504 (60)
US 1999-158700P 19991008 (60)
US 1999-138156P 19990607 (60)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Venkat, Jyothsna; Assistant Examiner: Koroma, Barba M.
LREP Silva, Robin M., Kosslak, Renee M., Flehr Hohbach Test Albritton & Herbert LLP
CLMN Number of Claims: 8
ECL Exemplary Claim: 1
DRWN 4 Drawing Figure(s); 3 Drawing Page(s)
LN.CNT 2210
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to the use of protein design automaton (PDA) to generate computationally prescreened secondary libraries of proteins, and to methods and compositions utilizing the libraries.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . each variable residue position as either a core, surface or boundary residue. The analyzing step may include a Dead-End Elimination (**DEE**) computation. Generally, the analyzing step includes the use of at least one scoring function selected from the group consisting of. . .

DETD . . . the calculations either unwieldy or impossible in real time. Accordingly, to solve this combinatorial search problem, a "Dead End Elimination" (**DEE**) calculation is performed. The **DEE** calculation is based on the fact that if the worst total interaction of a first rotamer is still better than. . . rotamer cannot be part of the global optimum solution. Since the energies of all rotamers have already been calculated, the **DEE** approach only requires sums over the sequence length to test and eliminate rotamers, which speeds up the calculations considerably. **DEE** can be rerun comparing pairs of rotamers, or combinations of rotamers, which will eventually result in the determination of a. . .

DETD . . . found, a Monte Carlo search may be done to generate a

rank-ordered list of sequences in the neighborhood of the **DEE** solution. Starting at the **DEE** solution, random positions are changed to other rotamers, and the new sequence energy is calculated. If the new sequence meets. . .

DETD . . . in U.S. Ser. No. 7,926, U.S. Pat. No. 6,296,312 a PCT US98/0725 4, preferred embodiments utilize a Dead End Elimination (**DEE**) step, and preferably a Monte Carlo step.

DETD . . . these methods, including, but not limited to, enzyme activity, stability, solubility, aggregation, binding affinity, binding specificity, substrate specificity, structural integrity, **immunogenicity**, toxicity, generate peptide and peptidomimmetic libraries, create new antibody CDR's, generate new DNA, RNA bindings, etc.

DETD . . . have residues in the hydrophobic cores screened, to prevent changes in the molecular surface of the protein that might induce **immunogenic** responses. Therapeutic proteins can also be designed in the region surrounding their binding sites to their receptors. Such a region. . .

DETD . . . antibodies, if the desired epitope is small, the library protein may be fused to a carrier protein to form an **immunogen** . Alternatively, the library protein may be made as a fusion protein to increase expression, or for other reasons. For example,. . .

DETD . . . members (for example, its substrates, if it is an enzyme), activity profiles, stability profiles (pH, thermal, buffer conditions), substrate specificity, **immunogenicity**, toxicity, etc.

DETD The Dead End Elimination (**DEE**) optimization method (see reference) was used to find the lowest energy, ground state sequence. **DEE** cutoffs of 50 and 100 kcal/mol were used for singles and doubles energy calculations, respectively.

DETD Starting from the **DEE** ground state sequence, a Monte Carlo (MC) calculation was performed that generated a list of the 1000 lowest energy sequences.. . .

L2 ANSWER 12 OF 34 USPATFULL
AN 2002:92254 USPATFULL
TI Protein design automation for protein libraries
IN Dahiyat, Bassil I., Los Angeles, CA, UNITED STATES
Hayes, Robert J., Altadena, CA, UNITED STATES
Bentzien, Joerg, Pasadena, CA, UNITED STATES
Fiebig, Klaus M., Frankfurt, GERMANY, FEDERAL REPUBLIC OF
PI US 2002048772 A1 20020425
AI US 2001-782004 A1 20010212 (9)
PRAI US 2000-181630P 20000210 (60)
DT Utility
FS APPLICATION
LREP FLEHR HOHBACH TEST, ALBRITTON & HERBERT LLP, Suite 3400, 4 Embarcadero Center, San Francisco, CA, 94111-4187
CLMN Number of Claims: 9
ECL Exemplary Claim: 1
DRWN 7 Drawing Page(s)
LN.CNT 3353
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to the use of protein design automation (PDA) to generate computationally prescreened secondary libraries of proteins, and to methods and compositions utilizing the libraries.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . the calculations either unwieldy or impossible in real time. Accordingly, to solve this combinatorial search problem, a "Dead End Elimination" (**DEE**) calculation is performed. The **DEE** calculation is based on the fact that if the worst total interaction of a first rotamer is still better than. . . rotamer cannot be part of the global optimum solution. Since the energies of all rotamers have already been calculated, the **DEE** approach only requires sums

over the sequence length to test and eliminate rotamers, which speeds up the calculations considerably. **DEE** can be rerun comparing pairs of rotamers, or combinations of rotamers, which will eventually result in the determination of a. . .

DETD . . . found, a Monte Carlo search may be done to generate a rank-ordered list of sequences in the neighborhood of the **DEE** solution. Starting at the **DEE** solution, random positions are changed to other rotamers, and the new sequence energy is calculated. If the new sequence meets. . .

DETD . . . processing may occur. As outlined in U.S. Ser. No. 09/127,926 and PCT US98/07254, preferred embodiments utilize a Dead End Elimination (**DEE**) step, and preferably a Monte Carlo step.

DETD . . . used to rescore a library in order to eliminate proteins containing sequences which can potentially bind to MHC, i.e. potentially **immunogenic** sequences.

DETD [0087] In a preferred embodiment, a variety of filtering techniques can be done, including, but not limited to, **DEE** and its related counterparts. Additional filtering techniques include, but are not limited to branch-and-bound techniques for finding optimal sequences (Gordon. . .

DETD . . . these methods, including, but not limited to, enzyme activity, stability, solubility, aggregation, binding affinity, binding specificity, substrate specificity, structural integrity, **immunogenicity**, toxicity, generate peptide and peptidomimmetic libraries, create new antibody CDR's, generate new DNA, RNA bindings, etc.

DETD . . . have residues in the hydrophobic cores screened, to prevent changes in the molecular surface of the protein that might induce **immunogenic** responses. Therapeutic proteins can also be designed in the region surrounding their binding sites to their receptors. Such a region. . .

DETD . . . antibodies, if the desired epitope is small, the library protein may be fused to a carrier protein to form an **immunogen** . Alternatively, the library protein may be made as a fusion protein to increase expression, or for other reasons. For example,. . .

DETD . . . members (for example, its substrates, if it is an enzyme), activity profiles, stability profiles (pH, thermal, buffer conditions), substrate specificity, **immunogenicity**, toxicity, etc.

DETD [0254] Dead End Elimination (**DEE**) optimization method (see reference) was used to find the lowest energy, ground state sequence. **DEE** cutoffs of 50 and 100 kcal/mol were used for singles and doubles energy calculations, respectively.

DETD [0255] Stating from the **DEE** ground state sequence, a Monte Carlo (MC) calculation was performed that generated a list of the 1000 lowest energy sequences.. . .

L2 ANSWER 13 OF 34 USPATFULL
AN 2002:16900 USPATFULL
TI Design and discovery of protein based TNF-alpha variants for the treatment of TNF-alpha related disorders
IN Dahiyat, Bassil I., Los Angeles, CA, UNITED STATES
Filikov, Anton, Monrovia, CA, UNITED STATES
PI US 2002009780 A1 20020124
AI US 2001-798789 A1 20010302 (9)
PRAI US 2000-186427P 20000302 (60)
DT Utility
FS APPLICATION
LREP FLEHR HOHBACH TEST ALBRITTON & HERBERT LLP, Four Embarcadero Center, Suite 3400, San Francisco, CA, 94111
CLMN Number of Claims: 13
ECL Exemplary Claim: 1
DRWN 21 Drawing Page(s)
LN.CNT 3189
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention relates to novel proteins with TNF-.alpha. antagonist activity and nucleic acids encoding these proteins. The invention further relates to the use of the novel proteins in the treatment of TNF-.alpha. related disorders, such as rheumatoid arthritis.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . the calculations either unwieldy or impossible in real time. Accordingly, to solve this combinatorial search problem, a "Dead End Elimination" (**DEE**) calculation is performed. The **DEE** calculation is based on the fact that if the worst total interaction of a first rotamer is still better than. . . rotamer cannot be part of the global optimum solution. Since the energies of all rotamers have already been calculated, the **DEE** approach only requires sums over the sequence length to test and eliminate rotamers, which speeds up the calculations considerably. **DEE** can be rerun comparing pairs of rotamers, or combinations of rotamers, which will eventually result in the determination of a. . .

DETD . . . found, a Monte Carlo search may be done to generate a rank-ordered list of sequences in the neighborhood of the **DEE** solution. Starting at the **DEE** solution, random positions are changed to other rotamers, and the new sequence energy is calculated. If the new sequence meets. . .

DETD . . . processing may occur. As outlined in U.S. Ser. No. 09/127,926 and PCT US98107254, preferred embodiments utilize a Dead End Elimination (**DEE**) step, and preferably a Monte Carlo step.

DETD . . . used to rescore a library in order to eliminate proteins containing sequences which can potentially bind to MHC, i.e. potentially **immunogenic** sequences.

DETD [0073] In a preferred embodiment, a variety of filtering techniques can be done, including, but not limited to, **DEE** and its related counterparts. Additional filtering techniques include, but are not limited to branch-and-bound techniques for finding optimal sequences (Gordon. . .

DETD . . . vaccines include a gene encoding an adjuvant molecule with the DNA vaccine. Such adjuvant molecules include cytokines that increase the **immunogenic** response to the variant TNF-.alpha. polypeptide encoded by the DNA vaccine. Additional or alternative adjuvants are known to those of. . .